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Editorial

What is the definition of "vitamin D deficiency" and who is considered "vitamin D deficient"? Urgent need for a national consensus

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Since early works on isolation and characterization of vitamin D by Elmer Verner McCollum and Edward Mellanby in 1900s, this molecule still seems mysterious (1-2). After several decades since discovery of the miraculous effect of cod liver oil in treatment of nutritional rickets, escalating number of reports provide a huge body of evidence for various effects of vitamin D on human body (3). The spectrum of vitamin D health effects is quite wide, from bone and muscles (so-called calcemic effects) to a variety of non-calcemic effects including cardiovascular, insulin function, adipogenesis, obesity, immunity and mental status. Consequently, having an optimal vitamin D status has attracted a huge attention (4-8).

Despite the fact that the body is equipped with the vitamin D photosynthetic machinery, undesirable vitamin D status is a global health problem due to many geographical, environmental as well as socio-cultural reasons (9-10). However, unlike most other nutrients, there is no consensus on definition of “desirable vitamin D status”. It is generally accepted that circulating 25-hydroxycalciferol (25(OH)D) concentration can well reflect the body's vitamin D status (11). However, there is no agreement on desirable serum 25(OH)D level (12). While some scientific bodies recommend concentrations above 50 nmol/L (13), some vitamin D experts criticize this recommendation and suggest as high concentrations as 75 and 100 nmol/L and even above (10). As a result, different research groups usually based on their experience, recommendation of the manufacturers of the commercial assay kits and occasionally their tastes use various cutoff points to define vitamin D status of their study population. Needless to say that the occurrence rates reported by these studies may hardly be comparable. The problem of definition of vitamin D status becomes even more complicated when considering the effect of assay system on 25(OH)D test results (14).

Table 1 shows some of the cross-sectional researches preformed over a decade ago. The cutoffs used, range from 23 nmol/L (15) to as high as 87.5 nmol/L (16). Interestingly the prevalence of undesirable vitamin D status in 20-64 yr males based on 23 nmol/Lwas reported 81.3% (15) while in another study on mothers of newborns, the prevalence rate was as low as 5.7%, based on 25(OH)D<50 nmol/L (17). Part of these discrepancies might be due to the methods used in various studies. Disagreement of 25(OH)D assay results obtained from different assay systems has been already reported (14, 18-22). This could potentially disturb decision making at the clinical settings (23).

At the national level, two nationwide surveys on vitamin D are noticeable. In 2001, the first National Integrated Micronutrient Survey (NIMS I), reported the prevalence rates of undesirable vitamin D status among 15-23 month children and pregnant women as 3.7% and 0.9%, respectively (24). However, after a decade the prevalence rates in these age groups tremendously increased to 23.7% and 86%, respectively, as reported by NIMS II (25). These unexpectedly worrying numbers vigorously stimulated stake-holders at Deputy of Health of the

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Iran Ministry of Health (MOH) to hold several sessions in order to take an urgent action. These sessions led to recommendations and implementations of supplementation for different population subgroups across the country.

Table 1. Occurrence rates of undesirable vitamin D status using different assay methods in different Iranian subpopulations

Author, year	Population	Method	Cutoff	Prevalence of undesirable vitamin D status
Moussavi M, [et al], 2005 (43)	153 boys and 165 girls, aged 14-18 yr	RIA	< 50 nmol/L	all subjects: 46.2% (72.1% in females and 18.3% in males)
Hashemipour S, [et al], 2004 (15)	1210 subjects 20-64 yr	RIA	Normal range: 23 to 113 nmol/L	81.3%
Salek M, [et al], 2008 (17)	88 newborns and their mothers	RIA	Mothers: < 50 nmol/L Newborns: < 31.2 nmol/L	Mothers: 5.7% Newborn: 4.5%
Kazemi A, [et al], 2009 (44)	67 full-term pregnant mothers	-	< 25 nmol/L	86% of the women and 75% of the newborns during winter and 46% of the mothers and 35% of the newborns during summer
Rahnavard Z, [et al], 2010 (16)	2396 healthy men	EIA	< 87.5 nmo/L	68.8%
Hovsepian S, [et al], 2011 (45)	1,111 healthy people-243 men and 868 women, 20-80 yr	RIA	< 75 nmol/L	70.4%
Kashi Z, [et al], 2011 (46)	351 subjects (66.4% women, 33.6% men) aged 11 to 69	EIA	< 75 nmol/L	87.5% in winter and 78.6% in summer
Kaykhaei MA, [et al], 2011 (47)	993 apparently healthy subjects	ECL	< 75 nmol/L	94.7%
Khalesi N, [et al], 2012 (48)	100 neonates and their mothers	Not reported	Not reported	85% of neonates and 74% of mothers
Neyestani TR, [et al], 2012 (27)	1111 children aged 9-12 yr	EIA	< 50 nmol/L	91.7 %
Talaei A, [et al], 2012 (49)	420 students 10-16 yr	RIA	< 50 nmol/L	84%
Alipour S, [et al, 2014 (50)	538 women aged 20-80 years	ECL	<35 nmol/L	69%
Faghih S, [et al], 2014 (51)	254 university students (19-32 yr)	RIA	< 75 nmol/l	95.2% of males 97.5% of females
Saki F, [et al], 2015 (29)	children (n=477) aged 9-18 years	HPLC	< 75 nmol/L	96%
Abbasian M, [et al], 2016 (52)	284 pregnant women and their newborn	EIA	< 75 nmol/L	Mothers: 61.3% Neonates: 51.4%
Larijani B, [et al], 2016 (30)	444 middle and high school students	EIA	< 75 nmol/L	77.6%

Abbreviations: ECL: electrochemiluminescence; EIA: enzyme immunoassay; HPLC: high-performance liquid chromatography; RIA: radioimmunoassay.

Notwithstanding, some points have seemingly been overlooked in interpretation of NIMS II findings. Firstly, the 25(OH) D assay method used in NIMS I was radioimmunoassay (RIA) whereas in NIMS II was electrochemiluminescence binding immunoassay (ECLIA) using Elecsys system. Disagreement among different 25(OH) D systems has been demonstrated in several studies which was more prominent for RIA than the other systems (19-20, 22). More importantly, the cutoffs used to define vitamin D deficiency in NIMS I was 25(OH)D < 12 and <25 nmol/L while in NIMS II was <25 and <50 nmol/L for vitamin D deficiency and insufficiency, respectively (24-25). Obviously, this rise in cutoff points could cause a great increment in the prevalence rates.

The National Food and Nutrition Surveillance (FNS) revealed 93% of the Iranian children have suboptimal circulating 25(OH) D (< 50 nmol/L) during cold seasons (26). This occurrence rate is quite comparable with our earlier reports from Tehran children (27). Similar occurrence rates were observed in adults across latitudinal gradient (28). In these studies similar cutoff points and assay methods were employed. Other studies that used similar cutoffs but different assay systems reported different occurrence rates in almost similar age groups (29-30).

Though lots of reports suggest a pandemic of vitamin D deficiency (31-36), some researchers believe that this is a misconception (37). They believe that the Institute of Medicine (IOM) recommendation for desirable circulating 25(OH) D concentration is based on recommended daily intake (RDA) for vitamin D. However, RDA considers the population at the highest end of distribution whereas estimated average requirement (EAR) gives a more realistic picture of the population's requirement. It is noteworthy that neither RDA nor EAR considers solar exposure. According to these researchers, based on EAR half of the population would need to have circulating 25(OH)D ≤ 40 nmol/L (16 ng/mL) (37). A major critique of this notion is that only calcemic effects of vitamin D were considered. Besides, it has been estimated that daily intake of 440 IU vitamin D (=11 µg) would result in 19.4 (CI: 13.9-24.9) nmol/L increment in serum 25(OH)D (38). Therefore, daily intake of vitamin D as much as RDA (600 IU) and EAR (400 IU) would result in an average increase of 26.4 and 17.6 nmol/L in circulating calcidiol. That means neither RDA nor EAR would be efficient in raising serum calcidiol concentrations to as high as 50 and 40 nmol/Lrespectively. at least in those people who do not have enough solar exposure for any reason.

The situation therefore seems absolutely confounding. The key question is raised as "what is the definition of vitamin D deficiency?" In other words, which criteria are mostly suitable for the Iranian population? Answer to this question is undisputedly important. One of the viable and sustainable strategies to tackle micronutrient deficiencies (including vitamin D) is fortification of staple foods (39). Without a concrete criterion, it would be hard, if not impossible, for stake-holders to decide how to implement and how to evaluate the effectiveness of the fortification program.

The other important issue is the variability of calcidiol assay results from different assay systems. To overcome this problem, employment of assay-specific cutoff points (40) as well as harmonization and standardization of the assay results have been proposed (41-42). Based on our experience, we believe that circulating 25(OH)D concentrations of 50 nmol/L (20 ng/mL) and above based on HPLC assay system could be considered adequate. This cutoff point could vary according to the assay system (42). Nevertheless, a national consensus is urgently needed on definition of adequate vitamin D status. Until that day, that we do hope it comes very soon, the establishment of a sustainable effective strategy against vitamin D deficiency is absolutely unrealistic.

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